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ORIGINAL STUDY

EVALUATION OF ASSOCIATION OF DIABETES MELLITUS WITH HEAD AND NECK CANCER: A CROSS-SECTIONAL STUDY

Dr. Amit Kumar, Dr. Gayathri Ramesh*, Dr. Vishal Chandra, Dr. Gaurav Rai, Dr. Antima Saxena***, Dr. Abhishek Anand******

Department of Oral and Maxillofacial Pathology, Rama Dental College Hospital and Research Center, Kanpur, India,

*Department of Dentistry, Chamarajanagar Institute of Medical Sciences, Yadapura Kasaba, Hobli, Chamrajnagar, India,

**Department of Oral and Maxillofacial Surgery, Buddha Institute of Dental Science and Hospitals, Kankarbagh; Patna, India,

Department of Public Health Dentistry, Institute of Dental Sciences, Siksha 'O' Anusandhan(Deemed to be University), Kalinganagar, Bhubaneswar, Odisha, India*Department of dentistry, Narayan medical College and Hospital, Sasaram, India

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Address for correspondence
Dr. Gayathri Ramesh, MDS.,
Associate Professor, Department of Dentistry,
Chamarajanagar Institute of Medical Sciences,
Yadapura Kasaba, Hobli, Chamrajnagar 571313, India
Email id-amug3r@gmail.com

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ABSTRACT

INTRODUCTION: Malignant neoplasm is a major cause of death in developed countries, and its incidence continues to grow. Diabetes mellitus is a serious and leading health problem. Recent studies demonstrated that Diabetes mellitus (DM) was associated with a higher risk of Head and Neck cancer. Only a few population-based studies, especially in Asian populations, have addressed these issues. Thus, this study aimed at assessing the relationship between Diabetes mellitus and Head and Neck Cancer (HNC) in reference to their socio-economic status.

MATERIALS AND METHODS: The present study was conducted on 483 HNC patients aged above 15 years. The data was collected from patients reporting to Mahavir Cancer Institute & Research Centre, Patna, and Rama Dental College Hospital and Research Center, Kanpur. Blood sugar level was tested to assess the status of diabetes mellitus. The demographic details such as place, social-economic status (SES), age and sex were recorded. Control group of 100 people aged above 15 years were selected with habits of using tobacco products and without any oral precancerous lesion/conditions. Odds ratios (OR) and 95% confidence intervals (CI) were estimated using unconditional logistic regression.

RESULTS: Of 483 patients, 70 patients (14.4%) had DM showing no overall relationship with HNC. A major number of HNC with DM was more in high socioeconomic status patients 41.7% ($p<0.05$), showing strong association whereas for low SES it was 3.4% ($p>0.05$). Out of overall Diabetes mellitus (DM), there were 77.1% of male and 22.8% were female.

CONCLUSION: Diabetes was weakly associated with HNC, but we observed evidence of a relationship with the socioeconomic group. People with HNC and low socioeconomic status showed less association with diabetes than people with high socioeconomic status.

KEY WORDS: Socioeconomic status, Diabetes mellitus, Head and Neck Cancer

INTRODUCTION

Cancer is a name given to group of diseases characterized by the growth of abnormal cells beyond their usual boundaries that can then invade adjoining parts of the body and/or spread to other organs. Other common terms used are malignant tumors and neoplasms. Cancer affects almost any part of the body and has many anatomic and molecular subtypes which force specific management strategies.

Cancer is second main cause of death globally and accounts for 8.8 million deaths in 2015. Lung, prostate, colorectal, stomach and liver cancer are the most common types of cancer in men, while breast, colorectal, lung, cervix and stomach cancer are the most common among women.[1]

An increasing figure of evidence advocates that certain types of cancer are more common in people with diabetes mellitus (DM).[2,3] Previous studies[4-7] report elevated risks of cancers of the liver, biliary tract, pancreas, stomach, colorectum, kidney, bladder, breast, and endometrium but a decreased risk of prostate cancer. Numerous mechanisms have been projected as part of the possible carcinogenic process in DM. For example, untreated hyperglycemia may contribute to tumor growth because of the increased need for glucose to fuel proliferation in neoplasms.[3] In patients with DM, a single hyperglycemia-induced process in which the mitochondrial electron transport chain overproduces superoxide and reactive oxygen species is generated.[1,8] Exposure to high levels of insulin and insulin-like growth factors (IGFs) in DM increases cellular proliferation and activation of the oncogenic epidermal growth factor receptor.[9] Additionally, IGF and its receptors have mitogenic and antiapoptotic effects and can be source of malignant transformation.[10,11]

Few studies with DM have also been related with HNC, these results are still debatable. In few studies,[12] DM patients had an increased risk of HNC cancer, while in other studies this risk was decreased. Some studies with DM have also been associated with HNC, these results are still controversial.[13] One of the possible explanations could be given for the inverse association between DM and HNC is the difference in their socioeconomic status.

This is the first study of its kind to study the association of diabetes and SES with HNC patients with effects of habits.

AIM AND OBJECTIVES

This study aims to evaluate the association between DM, HNC and SES of HNC patients.

MATERIALS AND METHODS

The present study was conducted on 500 Head & Neck cancer patients reporting at 2 different centers- - **Mahavir Cancer Institute & Research Centre**, Patna, and at **Rama Dental College Hospital and Research Center**, Kanpur. Out of which 17 cases was rejected due to insufficient data. The number of cases included were only 483 in this study. The control group included age and gender-matched 100patients with habits without any potentially malignant diseases (PMD). Informed consent was obtained from the patient. Ethical clearance was taken from Rama Dental College, Hospital and Research Centre, Kanpur and **Mahavir Cancer Institute & Research Centre**, Patna. Inclusion criteria included patients of age group above 15 years of both genders with tobacco habits and diagnosed for oral cancer. Patients below 15 years of age, patients with any other systemic conditions and on any medication affecting blood glucose levels and patients having any PMD's were excluded.

Participants were interviewed using a standardized questionnaire to collect information about age, sex, DM and social economic status (SES), tobacco consumption, and alcohol consumption Blood samples were collected from cases and controls and fasting blood glucose levels and 2hr postprandial levels were estimated. Glucose oxidase - peroxidase GOD/POD method was used for the estimation of glucose levels. It was based on Trinder's method. According to the American Diabetes Association (ADA) 2018 Guidelines it was considered positive for diabetes when values were FPG ≥126 mg/dL (7.0mmol/L)* (Fasting is defined as no caloric intake for ≥8 hours) PG ≥200 mg/dL (11.1mmol/L) during OGTT (75g)* Using a glucose load containing the equivalent of 75g anhydrous glucose dissolved in water.

STATISTICAL ANALYSIS

All the findings were entered in Microsoft Excel using SPSS 20.0 software and Odds ratios (OR) and 95% CI were estimated using unconditional logistic regression. The degree of freedom between variables were also observed. P-value < 0.05 represents statistically significant and P-value > 0.05 represents statistically non-significant.

RESULTS

TABLE 1: Shows a total of 483 cases and 100 controls. Among these, cases with tobacco use and alcohol consumption were more likely to be males with 78.2%, while females comprised of 22.1%. About 50% of patients were of age between 50 to 64 years of age. Most (71.4%) cases were of squamous cell carcinomas. Approximately 30% of cases were diagnosed with cancers of the oro-pharynx and hypopharynx or larynx, and 70% of the cases were diagnosed with other cancers of the oral cavity

Table 2: It was found that diabetes mellitus (DM) was not associated with HNC in models adjusted for age, sex,

tobacco use, and alcohol (OR, 0.95; 95% CI, 0.83–1.08; Table 2). Results for minimally adjusted models were similar to results obtained with adjustment for age, race, sex, tobacco use and alcohol. ORs were slightly higher for women than for men, but a comparison of models with and without a product term for sex and diabetes yielded p=0.091. Overall Diabetes mellitus (DM) cases there were 77.1% male and 22.8% were female.

Table 3: In these table HNC cases were divided in respect to their SES cases. Low SES were 71.2% of total cases in which diabetes mellitus (DM) cases were only 3.4% with p-value being 0.771. This showed no relationship with HNC while cases which were high of SES were 28.7%, butonly DM cases in them were 41.7%. among the controls it was 17.1% with p-value of 0.021 that showed direct relationship with HNC.

DISCUSSION

483 HNC patients involved in the examination bunch were all priorly histopathological analyzed cases. Age sex and social economic status coordinated controls with harmful propensities and with no premalignant lesion were enrolled. HNC was significantly higher among patients aged between 50 to 64 years comprising around 50%.[14] Although a positive link between DM and many types of cancers

Table 1: Showing characteristics of the 483 cases and the 100 controls.

AGE	Cases		Controls	
	n (483)	%	n (100)	%
12–39	18	3.7	5	5
40–45	27	5.6	4	4
45–49	51	10.5	14	14
50–54	73	15.1	10	10
55–59	90	18.6	19	19
60–64	85	17.5	13	13
65–69	69	14.2	21	21
70–74	45	9.3	11	11
75–94	25	5.1	3	3
Sex				
Women	107	22.1	29	29
Men	378	78.2	71	71
Tobacco use status				
Never	9	1.8	00	00
User	474	98.1	100	100
Alcohol drinking status				

Never	93	19.2	28	28
User	390	80.7	72	72
Sub-site of tumour				
Oral cavity	368	69.3	00	00
Oro- and hypopharynx or larynx	148	30.6	00	00
Histology of tumour				
Squamous cell	388	80.3	00	00
Other	95	19.6	00	00
Previous systemic diseases				
Yes	103	21.3	23	23
No	380	78.6	77	77

Table 2: Shows adjusted odds ratios (OR) and 95% confidence intervals (CI) for the association between head and neck cancer and DM

DM	Case 483 n(%)	Control 100 n(%)	OR	95%CI	p-value*
All	70(14.4)	8(8)	0.95	0.83–1.08	0.091
Women	16(22.8)	1(12.5)	1.06	0.82–1.38	0.078
Men	54(77.1)	7(87.5)	0.91	0.79–1.06	0.052

Table 3: Shows adjusted odds ratios (OR) and 95% confidence intervals (CI) for the association between head and neck cancer and DM in reference with SOCIAL ECONOMIC STATUS (SES)

SOCIAL ECONOMIC STATUS (SES) n (%)	Case 483 n (%)	Control 100n (%)	OR	95%CI	p-value*
Low SES	344(71.2)	65(65)	1.498	0.84-2.10	0.025
Diabetes	12(3.4)	2(3.07)	1.24	0.27-5.66	0.771
Men	8(66.6)	2(100)	3.58	1.17-6.94	0.001

Women	4(33.3)	0	1.88	0.10-35.3	0.673
High SES	139(28.7)	35(35)	0.75	0.361-1.57	0.457
Diabetes	58(41.7)	6(17.1)	1.55	1.070-2.24	0.021
Men	46(79.3)	5(83.3)	3.358	1.726-7.16	0.003
Women	12(20.6)	1(16.6)	2.25	0.32-19.2	0.372

DM exceptionally type 2 is considerably more identified with way of life. It was found that DM prevalence was high in High SES individuals in comparison to Low SES this is because DM is a life style disease which is influenced by age kind of food habbit BMI weight, central obesity and physical exercise is significant hazard factor for it[24]. So, in this current investigation as a result of these realities we isolate our cases into social economic status. At the point when we isolated this information into social economic status we found that 71.2 individuals were of Low SES and 28.7% were High SES a The explanation could be that HNC in India is primarily because of smokeless tobacco like khaini zarda, etc and areca nut like panmasal (This item without tobacco is known as 'panmasala' while the item with tobacco is known as 'gutkha)'[25] smoke tobacco like bidi (Indian explicit non-filtered cigarette) which are broadly devoured by individuals who are in Low SES like work class, vegetable vendor, cart puller and so forth due to their work pressure and because of bidi being less expensive then cigarettes. Whereas smoke tobacco like cigarette are favored by high SES individuals. In India, where oral cancer growth is a striking frequency, just short of what one-fifth (19%) of tobacco consumed is in form of cigarettes.[26]

Around 26% of all adults in India use Smokeless tobacco by chewing, applying it to the teeth and gums, or by sniffing. Consumption of smokeless tobacco (SLT) (26%) is more prevalent than various smoking tobacco. Of the 26% of all adults who use SLT, 21% use SLT every day and the other 5% use it occasionally. A little additional than 2% of the adults who were SLT users in the past, either daily or occasionally, have since stopped such use completely. Use of SLT amid males (33%) is higher than females (18%); in contrast, smoking has a sharp difference between the two genders. In rural areas, 29% of adults use SLT, whereas the figure is 18% in urban areas is as per WHO in India 27

There are very few studies done similar to the present study and hence comparison in detail is limited.

Survey by Corsi and Subramanian in 2014 evaluated socioeconomic differences in smoking behavior among males in India and reported that people who were wealthier, more educated, and having a decent job were more prone to cigarette smoking, and on the other side, people who are less educated with poor socioeconomic status had a habit of bidi smoking. This rare difference in socioeconomic inclines in consumption of two smoking habits reported among the males raises serious concern and curiosity to tackle this problem. Also, a greater concern that is ignored in many studies is growing prevalence of dual tobacco consumption amid the population and forming a tobacco quit strategy.[28]

Studies confirm that people consuming smokeless tobacco and bidi are at more risk of developing HNC then people consuming filtered cigarettes in India[26,29,30] This clearly shows HNCare much more prone to people of low SES then High SES.

By the above conversation 2 focuses are clear, one DM is identified with High SES on account of their way of life and second is HNC is increasingly inclined in LOW SES individuals since utilization of smokeless tobacco and bidi smoking.

So in this current investigation, it was discovered that in 71.2% of instances of HNC were of Low SES and just 12 instances of DM were discovered that is just 3.4% p-value 0.77 demonstrating no applicable connection among HNC and DM. Very little investigation has been done till date including this subject so there isn't a lot of study accessible to talk about with results obtained t in this examination.

While in High SES instances of HNC were 28.7% in which 41.7% cases were of DM which show affiliation DM with HNC p-value 0.021

By this above conversation we can say that DM is way of life ailment so its less pervasive in Low SES individuals and HNC is progressively regular in Low SES. So when we look generally HNC isn't related with DM yet when we find in individuals With High SES where DM is basic in them HNC is related with DM.

This can be comprehended by pathogenesis of Diabetes mellitus and malignant growth. They are multifactorial maladies; a few potential pathophysiological pathways can add to their reliance. Nonetheless, most components fundamental the relationship among DM and the ensuing

advancement of HNC stay hazy. A likely reason for the expanded danger of HNC in patients with recently analyzed DM may be shared hereditary hazard factors, DM-related metabolic morbidities (eg, hypertension and dyslipidemia), stoutness, maturing, and sex as the connection among DM and other cancers.[32,33]

Epigenetic adjustments of the acquired or obtained hereditary changes in disease may give another conceivable component connecting the reasons for disease and DM.[34] For instance, RRAD (OMIM 179503), an individual from the Ras-related GTPase superfamily, is every now and again methylated in various human dangerous tumors.[35] In human malignancies, RRAD may assume inverse jobs as an oncogene or a tumor silencer, contingent upon the malignancy and cell type. *RRAD* has been suggested to be a tumor suppressor gene in several human malignant tumors, including malignant mesothelioma, lung cancer, breast cancer, cervical cancer, prostate cancer, and NPC.[37]*RRAD* is epigenetically inactivated in NPC. Epigenetic down-regulation of *RRAD* might disrupt the pathways downstream of the tumor suppressor p53 and lead to a malignant and aggressive phenotype.[36] Conversely, RRAD translocates Grap2 and GCIP from the core to the cytoplasm, in this manner hindering the tumor silencer movement of GCIP, which happens in the nucleus.[38] Consequently, *RRAD* may promote carcinogenesis at least in part by inhibiting GCIP-mediated tumor suppression.

One possible mechanism that links DM to the development of HNC is long-term exposure to hyperinsulinemia, which leads to breast cancer. Insulin is a potent growth factor that promotes proliferation and carcinogenesis in various ways, directly and through IGF.[34-36] Another reasonable explanation is hyperglycemia, which may directly promote tumors: cancer cells rely on increased glucose consumption.[39] The literature also reports that hyperglycemia induces DNA damage, down-regulate the expression of antioxidants, and increases the generation of reactive oxygen species.[40]

This is the primary investigation corresponding the relationship of DM and HNC concerning their social monetary status and first of its sort.

CONCLUSION:

we reason that DM isn't related to HNC by and large yet as we realize that some place frequency of DM relies upon way of life of an individual and HNC is progressively inclined in Low SES individuals and these individuals have low occurrence of DM and in high SES individuals DM is related with HNC. This is just on the grounds that number instances of DM is more in High SES individuals. Further broad investigation is required with enormous example size to get increasingly productive connection.

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CONFLICTS OF INTEREST:

There are no conflicts of interest.

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